GPhA
Generic Pharmaceutical Association

1620 I Street, NW • Suite 800 • Washington, DC 20006
202-833-9070 • Fax: 202-833-9612 • Email: info@gphaonline.org

September 19, 2002

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane
Room 1061 – HFA-305
Rockville, MD 20852

Re: Docket No. 02D-0350
Guidance for Industry
Handling and Retention of BA and BE Testing Samples

Dear Sir or Madam:

On behalf of the Generic Pharmaceutical Association (GPhA), I submit the following comments on the Guidance for Industry Handling and Retention of BA and BE Testing Samples.

GENERAL COMMENTS:

1. Because this guidance will apply both to ANDAs and NDAs, GPhA recommends that it be moved from the "Generics" section of FDA's Guidance web page to the "Biopharmaceutics" section.

2. The scope of this guidance should be clarified in that there should be no sample retention requirement for studies not used to support an application (e.g., pilot studies and failed BE studies for ANDAs). For NDAs, where all studies, including pilot studies, must be submitted, the sample retention requirement should apply only to pivotal studies, not supportive studies.

3. For placebo-controlled studies (e.g., clinical endpoint BE studies), GPhA recommends requiring retention samples of the placebo as well as the test and reference products.

4. The draft guidance does not mention how long retention samples must be kept. GPhA believes that the sample retention times cited in 21CFR 320.38 and 21CFR 320.63 should be added to the guidance.

5. GPhA recommends clarifying the amounts of sample to be retained. The draft guidance allows for significant uncertainty regarding the amount of sample to be

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retained. The phrase "five times all of the release tests" could be interpreted in a number of ways. For example, dissolution testing could require 6, 12, or 24 units, depending on the outcome of the test. Similarly, content uniformity testing could require 10 or 30 units. GPhA recommends calculating the amount of retention sample based on the smallest amount for each test (e.g., 6 units for dissolution, and 10 for content uniformity). These could be characterized as the amounts typically required for routine testing.

For reference products, the amount required for full release testing is generally not known. Often, for USP articles, generic drug manufacturers subject their products to additional testing beyond that specified in the USP monograph (e.g., impurities, water, etc.), so it is unclear whether the number required should be calculated from the USP monograph or the Sponsor's test methods. Sometimes, sponsors employ methodology different from that of the USP monograph, resulting in different numbers of dosage units required for retention depending on the method used. Finally, some USP tests require exorbitant numbers of dosage units (e.g., where the active ingredient is extracted and subjected to IR or melting point identification tests). Because of the high cost of some reference products ($50/dosage unit or more in some cases), it is important to define the amounts more precisely.

Given this backdrop, GPhA also recommends setting an upper limit on the number of dosage units required, perhaps 200 in the case of solid oral dosage forms. A suitable phrase would then be "for solid oral dosage forms, five times the amount required for routine release testing, or 200 dosage units, whichever is less." Similar upper limits should be developed and specified for other common dosage forms, such as oral liquids, reconstitutable powders, creams, ointments, etc. Adding a few worked examples to the guidance may also be useful.

6. For multi-site studies, the guidance should specify that the total amount to be retained among all of the sites should satisfy the "five times" requirement. It would be an undue burden on the industry to require each site in a multi-site study to retain the full "five times" amount.

7. For multi-site studies in which the retention samples are shipped to an independent third party, GPhA believes that the third party should segregate the samples from the various sites so that any given retention sample can be unambiguously associated with the site from which it came.

8. The guidance should specifically permit the inclusion of opened containers for retention samples. For example, if tablets for dosing were withdrawn from a bottle, then the remainder of that bottle together with one or more others ought to be acceptable.

9. The guidance does not specify what material should be retained in the case of a reference standard that is an extemporaneously compounded solution or suspension,

as is commonly the case for BA studies. Neither does the guidance specify what form should be retained in the case of reconstitutable powders (e.g. for oral suspensions). GPhA recommends that for each of the cases cited, the form provided by the sponsor should be the one retained. Thus, for an extemporaneously compounded oral solution or suspension, the pure active ingredient should be retained, not the final compounded solution or suspension. Likewise, for reconstitutable powders, the unreconstituted powder should be the form retained, not the reconstituted oral suspension.

10. GPhA recommends excluding population pharmacokinetic studies performed on patients enrolled in clinical trials from the sample retention requirements.

SPECIFIC COMMENTS:

GPhA also offers the following specific changes and recommendations:

Lines 168-169:

GPhA recommends deleting the parenthetical phrase "(The following text has been excerpted from the preamble of the final rule; bolded text is particularly relevant.)". Several minor changes to the excerpted text need to be made (*vide infra*); therefore, it would not be an exact quote from the preamble.

Line 191-200:

GPhA recommends changing the phrase "unit dose" to read "unit of use", because clinical supplies for a blinded study are not necessarily supplied in unit dose packaging.

The case where the clinical supplies are packaged according to block randomization with a small block size (e.g., 3) should be addressed. Such schemes are useful to ensure balance in a stratified study. In an example of such a scenario, one test treatment, one reference treatment, and a placebo treatment would all be grouped together as a set (block) of three (although the identity of each would be hidden). The retention sample would then be a sufficient number of blocks (of 3 treatments), randomly selected, to satisfy the "five times" requirement for each treatment. The identity of the treatments in the retention samples would remain hidden (until the randomization code was broken during FDA sample collection), but exactly equal numbers of units of each treatment (and placebo) would be assured. A block size of 3 is the most common, but the concept applies to any small block size.

Lines 198-200, 331-335:

Because the guidance permits sample retention at a third party facility, GPhA recommends broadening this sentence to specify maintaining the sealed code at the

facility where the retention samples are stored (possibly an independent third party site), rather than at the testing facility.

Lines 202-211:

This section is written for the case where both the test and reference products are used for more than one study. It should be broadened to allow for the case where either is used for multiple studies. For example, a single reference lot may be used for several studies involving different test lots.

The case where a single CRO with multiple clinics conducts two or more studies on the same test and reference product should be addressed. For example, if a single CRO conducts a fasting BE study in their clinic in one state, and a fed BE study on the same test and reference product in their clinic in a different state, it should be permissible to retain a single set of retention samples (i.e., 5 X full monograph testing) at one of the two clinics.

The case where a single study is used to support more than one application should also be addressed. In such a case, a single set of retention samples (i.e., 5 times release testing) should be retained. Furthermore, the retention period should be the first one to expire (e.g., 5 years following approval of the earlier application).

Lines 247-256, 279-283, 293-297, 333-335, 429-431:

Based on member experience, it appears that the Agency considers contract packagers of clinical supplies not to be independent third party sites. Apparently the Agency does not want retention samples to be returned from clinical sites to the same contract packager that packaged them. If this is the case, these sections should be clarified to reflect this point.

Lines 281-283:

GPhA recommends deletion of the phrase "following completion of the study" to permit the investigators at the clinical sites to select the retention samples and send them back to the SMO immediately for storage.

Line 302:

GPhA recommends deleting the phrase "and involve non-oral dosage forms" because clinical endpoint or pharmacodynamic BE studies may very well involve oral dosage forms.

Lines 370-385:

Pivotal in-vitro dissolution testing required for the approval of a product could be

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construed to be an "in-vitro BE study". Examples include comparative dissolution profile testing on non-biostudy strengths for the purposes of obtaining a biowaiver, dissolution profile testing to support a BCS waiver, and in-vitro dissolution testing used to support an ANDA on an AA rated product. GPhA believes that reference products for such in-vitro dissolution testing should be specifically exempted from the sample retention requirements in this guidance. Satisfying the "five times" sample retention requirement for all reference products used in pivotal comparative dissolution profile testing would pose an undue burden for industry and appears to serve no useful purpose. GPhA has no objection to retaining the "five times" amount of test product used for all pivotal comparative dissolution profile testing, because the test product is generally available in such quantities at no additional cost.

Line 458:

GPhA recommends using terminology that is broader in scope than "blood sampling". For example, testing facilities should include facilities that conduct urinary excretion studies, pharmacodynamic studies, clinical endpoint BE studies, etc.

GPhA appreciates your consideration of our comments. Please contact me, if you have any questions or need clarification.

Steve Bende, Ph.D.

Vice President
Science, Professional and Regulatory Affairs

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4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas

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7 Payment *Bill to:* Enter FedEx Acct. No. or C

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